NDA 20-896 / S-006, S-009

Hoffman-LaRoche Inc
340 Kingsland Street
Nutley, NJ 07110-1199

30 APR 2001

Attention: Murad Husain
Program Director

Dear Mr. Husain:

Please refer to your September 20, 1999 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for XELODA (capecitabine) tablets, 150 mg and 500 mg.

We acknowledge receipt of your October 30, 2000 submission and your November 6, 2000 and April 13, 2001 amendments that constituted a complete response to our September 20, 2000 action letter.

This supplemental new drug application provides for the use of XELOD as first-line treatment of patients with metastatic colorectal carcinoma when treatment with fluoropyrimidine therapy alone is preferred. Combination chemotherapy has shown a survival benefit compared to 5-FU/LV alone. A survival benefit over 5_FU/LV has not been demonstrated with Xeloda monotherapy. Use of Xeloda instead of 5FU/LV in combinations has not been adequately studied to assure safety or preservation of the survival advantage.

Additionally, we acknowledge receipt of your October 23, 2000 Changes Being Effected labeling supplement (S-009) and your November 28, 2000 amendment to add a Contraindication, Warning, a dosing instruction to increase the safe use of Xeloda, and safety instructions to patients in conjunction with a "Dear Doctor" letter regarding renal impairment.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text (attached). Accordingly, the supplemental applications are approved effective on the date of this letter.

As agreed to in our April 30, 2001 teleconferences, the final printed labeling (FPL) must be identical to the attached draft labeling. These revisions are terms of the approval of this application.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you

may submit 20 paper copies of the FPL as soon as it is available but no more than 30

days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplements NDA 20-896/S-006 and S-009." Approval of this submission by FDA is not required before the labeling is used.

In consultation with the Division of Drug Marketing, Advertising and Comunications (DDMAC), we stress the following points about the promotion of Xeloda for first-line treatment of colorectal cancer:

- All promotional materials and activities regarding the efficacy or use of Xeloda for first-line metastatic colorectal cancer must include the entire language of the indication section in the approved product labeling.

- Similarly, when promoting the efficacy and use of Xeloda in metastatic colorectal cancer, all promotional materials and activities must include information on the endpoint of survival. Survival is the primary endpoint of interest in first-line colorectal cancer and the primary basis of approval of this sNDA. Selective presentation of surrogate endpoints such as response rate and/or time to progression would be false and misleading. Moreover, minimization of the survival data could represent a public health and safety issue. In addition, please note that physicians and patients must be made aware that treatment exists that has demonstrated survival superior to the five-day regimen of 5-FU/LV. This information must be prominently presented in your promotional materials and activities.

- Furthermore, and as stated in the September 20, 2000 approvable letter, all promotional materials and activities must not present the differences in the safety profile between Xeloda and 5-FU/LV as an overall safety advantage for Xeloda Any suggestions or implications that Xeloda is better tolerated or has fewer side effects overall would be misleading. Advertising must include the incidence of all grades and of all grade 3 and 4 adverse events in the two arms of the randomized trials. Presentation of trends in overall gastrointestinal toxicities in favor of Xeloda must be accompanied by the data that the incidence of grade 3 and 4 diarrhea, nausea and vomiting were similar between the arms.

We remind you of your previous postmarketing study commitments in your October 30, 2000 submission. These commitments are listed below.

1. Update the survival analyses after a total of 1180 deaths have occurred in the two randomized controlled trials, SO14694 and SO14796.

   Estimated Updated Survival Analysis submission date: December, 2002

2. Submit the results of the M66002 and M66004 clinical trials in advanced metastatic colorectal cancer studying Xeloda in combination with irinotecan when completed. If other trials are initiated with this combination, please submit the results when available.

   Final Report Submission: M66002 to be submitted in July, 2002
   M66004 to be submitted in January, 2003

We acknowledge your April 30, 2001 teleconference commitment to address the additional Phase 4 requirements listed below.

1. Submit the final study report for #BP15831, "Comparison of the pharmacokinetics of capecitabine in Japanese and Caucasian cancer patients." We note that a retrospective analysis (report #B-164833) performed on pooled data from seven phase l studies suggested differences between these two populations.

   Final Report Submission: Late October, 2001

2. Identify and submit final study reports for all trials assessing the activity (phase 2) or efficacy (phase 3) of capecitabine as second-line therapy in patients with colorectal cancer previously treated with a fluoropyrimidine-based therapy.

   Final Report Submission: Late October, 2001

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to the sNDA (SE1-006). In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to the NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled '**Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on this application.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Oncology Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Maureen Pelosi, Project Manager, at (301) 594-5778.

Sincerely,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research